REMARKS

Upon entry of the present amendments Claims 70-79, 81, 83-114 will be pending in the subject application. Claim 78 is withdrawn from consideration. Claims 80 and 83 were previously canceled.

Claims 88 and 90 are amended in an effort to expedite prosecution. Without acquiescing to the propriety of any of the prior art rejections, the claims are now limited to human, chimeric or humanized antibodies or fragments thereof that bind to both of the Killer Ig-Like Receptors (KIRs) KIR2DL1 and KIR2DL2/3, and further provide that said human, humanized or chimeric antibody, or fragment thereof, is capable of neutralizing or inhibiting KIR-mediated inhibition of NK cell cytotoxicity of target cells by NK cells expressing any of the following (i) KIR2DL1, (ii) KIR2DL2/3 and (iii) a combination of KIR2DL1 and KIR2DL2/3. Claim 90 differs from claim 88 only in that it further requires that the antibody compete with DF200 for binding to KIR2DL1 and/or KIR2DL2/3. Antibodies or antibody fragments possessing these combination of properties are not taught or suggested by any of the cited references.

Claims 92-110 are newly presented. These claims further limit claims 88 and 90 in that they specify that the antibody or fragment thereof inhibits binding of HLA-C molecules to NK cells that express KIR2DL1 and/or KIR2DL2/3 or require the antibody to lack an Fc region.

In addition, several dependent claims recite that the antibody or fragment thereof promotes lysis of target cells by NK cells that express i) KIR2DL1, (ii) KIR2DL2/3 or (iii) a combination of KIR2DL1 and KIR2DL2/3, and further provide for the NK cells to bind specific HLA-C ligands in the absence of the antibody with binding to said ligands inhibited by the antibody. Also, several dependent claims provide for the antibody, or antibody fragment containing compositions, to further comprise human immune cells. These claims include exemplary embodiments of the invention which find support in the as-filed application, as well as finding support in both provisional applications to which this application claims benefit of priority.

Also, Claims 111 and 112 are newly presented which further limit claims 88 and 90 by explicitly reciting that the claimed antibody or fragment not comprise an antibody or fragment containing the variable light chain polypeptide contained is in the NKVFS1 antibody. All of the newly submitted claims correspond to the elected subject matter, which is currently under active examination.

Claims 113 and 114 further limit the independent claims from which they depend by specifying that the antibody comprises a specific type of effector region.

Accordingly, upon entry of the present amendments, Claims 70-114 will be pending. Claims 70-77 and 79-114 should be subject to examination. Claim 78 stands withdrawn from consideration. Favorable consideration of all of the pending claims is respectfully requested.

At the outset, Applicants gratefully acknowledge the Examiner's withdrawal of the rejection under 35 U.S.C. § 103 (a) rejection based on US2005/0037002 (Velardi *et al).* and Eisenthal *et al.* . *(*J Immunol. 144:4463-4471(1990)); the rejection under 35 U.S.C. § 102(b) of Claims 88 and 90-91 over Kim et al. (J Immunol. 159:3875-3882 (1997)) as allegedly evidenced by Shin *et al.* (Hybridoma, 18(6)521-27 (1999)); and the rejection of claims 88 and 89 as allegedly being obvious over Kim et al. (J Immunol. 159:3875-3882 (1997)) in view of Harlow and Lane.

However, Claims 70-79, 81 and 83-91 still stand rejected based on alleged prior art. The specific grounds of rejection are respectfully traversed below.

Traversal of Rejection of Claims 88 and 90 Under 35 USC § 102 (b) As Assertedly Being Anticipated by Spaggiari et al., (Blood 99(5):1706-1714 (March 2002)) as Allegedly Evidenced by AbD Serotec and Statements in the Specification at Page 62.

Claims 88 and 90 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Spaggiari *et al.* (Blood, 2002, 99(5):1706-14 (March 2002)), hereinafter "Spaggiari *et al.*" as

allegedly substantiated by the AbD Serotec reference, hereinafter "Serotec," and the specification at page 62, lines 4-5 and 9.

Essentially the Examiner asserts that Spaggiari *et al.* teach an antibody, referred to as NKVFS1, which anticipates the antibody recited in claims 88 and 90, as allegedly supported by Serotec, and an alleged admission in the subject application on page 62 at lines 4-5 and 9. The rejection is respectfully traversed.

As noted above, independent Claims 88 and 90 are both amended without prejudice to recite that the claimed antibody or fragment is a human, humanized or chimeric antibody, or comprises a fragment of a human or humanized antibody, wherein the antibody or fragment, is capable of neutralizing or inhibiting KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing any of the following (i) KIR2DL1, (ii) KIR2DL2/3 and (iii) a combination of KIR2DL1 and KIR2DL2/3.

All of the newly presented claims depend from Claims 88 or 90. All of the pending claims are directed to an antibody or fragment that neutralizes or inhibits KIR-mediated inhibition of NK cells which express either or both of KIR2DL1 and KIR2DL2/3, and further require that the antibody comprises a human, chimeric or humanized antibody, or an antibody fragment that comprises a fragment of a human or humanized antibody that neutralizes or inhibits KIR-mediated inhibition of NK cells which express either or both of KIR2DL1 and KIR2DL2/3.

Applicants respectfully traverse the rejection of Claims 88 and 90 as allegedly anticipated by Spaggiari. As a preliminary matter, Applicants assert that Spaggiari is not a valid reference under 35 USC § 102(b). While the reference mentions an antibody named NKVFS1, there is no indication anywhere in the text of the reference that this antibody or a cell line that secretes the antibody was made publicly available, e.g., publicly deposited prior to the filing date of this application. Nor does the reference otherwise enable or describe this specific antibody so as to enable a skilled artisan to make this antibody or know that they are even in possession of this specific antibody or an equivalent. For example, the reference does not provide the specific

amino acid or nucleic acids encoding the variable regions of this antibody, nor does the reference disclose the CDRs of this antibody. Without this information, Spaggiari is respectfully submitted not to be a valid anticipatory reference, as it would not enable a skilled artisan how to make this antibody, nor would the reference allow a skilled artisan to be placed in possession of this antibody.

Serotec does not cure the deficiencies of Spaggiari *et al.* While Serotec suggests that a mouse anti-KIR monoclonal antibody referred to as NKVFS1 (which may or may not be the same antibody as the NKVFS1 antibody mentioned in Spaggiari) is apparently now commercially available, there is no evidence from this citation that the NKVFS1 antibody of Spaggiari was publicly available prior to the effective filing date of the claimed invention (July 2, 2003).

In addition, Applicants respectfully submit that Applicants' specification at page 62 does not establish the public availability of the NKVFS1 antibody. Applicants acknowledge that they conducted assays with this antibody and found that, under specific assay conditions, it competed with the DF200 antibody claimed herein. However, this does not provide evidence that NKVSF1 was publicly available prior to the present invention.

To the contrary, it was only after having made DF200 and further after the filing of the initial provisional application filed in September 2003, that Applicants obtained the NKVSF1 antibody under a Material Transfer and Use License Agreement (MTA). The MTA specified that NKVSF1 was provided to Applicants under confidence to be used solely in Applicants' laboratory, and did not permit the unrestricted transfer of NKVSF1 outside of Applicants' laboratory. Applicants are unaware of this monoclonal antibody being made publicly available prior to the filing date of this application. Accordingly, based on the foregoing, Spaggiari is respectfully submitted not to be a valid reference under 35 USC § 102(b), alone, or when considered with Serotec and/or Applicants' disclosure at page 62.

In addition, even if Spaggiari *et al.* were a usable reference, Applicants maintain that it does not anticipate Claims 88 and 90 as the NKVFS1 antibody disclosed in the reference is reported to be a mouse monoclonal antibody. By contrast, claims 88 and 90 (as well as the

claims dependent thereon) are all directed to a human, chimeric, or humanized antibody, or fragment of a human or humanized antibody, or a composition containing this antibody or fragment, wherein the antibody or fragment binds KIR2DL1 and KIR2DL2/3, and further wherein said antibody or fragment is capable of neutralizing or inhibiting KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing KIR2DL1 and/or KIR2DL2/3, or antibodies wherein said human, humanized or chimeric monoclonal antibody or fragment thereof competes for binding to said KIR2DL1 and/or KIR2DL2/3 on the surface of an NK cell. Spaggiari does not teach or suggest such any human, humanized or chimeric antibody or antibody fragment or an antibody that competes therewith. Accordingly, Applicants respectfully submit that the instant obviousness rejection of Claims 88 and 90 should be withdrawn.

In addition, the Spaggiari *et al.* reference does not anticipate Claim 110 as the NKVFS1 antibody disclosed in the reference is reported to be a mouse monoclonal antibody of mouse IgG2a isotype.

In addition, the Spaggiari *et al.* reference does not anticipate Claims 113 and 114 as the NKVFS1 antibody disclosed in the reference is reported to be a mouse monoclonal antibody of mouse IgG2a isotype. Because one of the goals of the invention is to block the interaction of an inhibitory KIR and its corresponding HLA ligand in vivo in order to potentiate NK cells, i.e. without depleting the NK cells, isotypes that mediate low effector function, such as IgG4 or antibodies lacking an Fc region, typically are preferred (see PCT application page 20 lines 25-27. It is noted additionally that the Spaggiari *et al.* reference does not suggest that NKVSF1 could capable of neutralizing or inhibiting KIR-mediated inhibition of NK cell cytotoxicity such that there would be no teaching toward selecting an antibody that does not substantially mediate effector function.

Traversal of Rejection of Claims 88, 90 and 91 Under 35 USC § 103 (a) As Assertedly Being Obvious Over Based on Shin et al., (Hybridoma, 18(6):521-527 (1999)) in view of Kim et al. (J Immunol. 159:3875-3882(1997)), and in view of Alleged Admissions in the Specification on page 25 at lines 15-28 and in the Paragraph Spanning pages 25-26.

Claims 88, 90 and 91 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Shin *et al.* (Hybridoma, 18(6):521-527 (1999)) (hereinafter "Shin *et al.*") in view of Kim *et al.* (J Immunol. 159:3875-3882(1997)) (hereinafter "Kim *et al.*"), and in view of alleged admissions in the specification on page 25 at lines 15-28 and in the paragraph spanning pages 25-26.

Particularly, the Office Action states the following:

> Shin *et al.*, teach that HLA-C recognizing receptor that is inhibitory is the p58 belonging to KIR2DL group comprised of KIR2DL1 and KIR2DL2/3 (especially paragraph spanning pages 521-522). Shin *et al.* teach that the mAb that has its epitope in the HLA binding region in p58 KIR may be the most effective mAb for blocking the interaction between KIR and HLA-C that it is known that both the γ2 and γ3 domains are involved in the interaction between p58 KIR and its ligand, HLA-C (especially second full paragraph at line 1, column 1 on page 526). Shin *et al* teach the method of mAb production via conventional hybridoma technology of Kohler and Milstein as well as methods for assessing the ability of the mAb to inhibit p58-mediated inhibition of NK cell cytotoxicity (especially materials and methods section).
>
> Shin *et al* do not exemplify wherein the anti-p58 mAb blocks the binding between p58 KIR and HLA-C, nor that it competes for binding with mAb DF200 to KIR2DL1 and/or KIR2DL2/3.
>
> Kim *et al* teach that a polypeptide consisting of the two extracellular Ig domains can be recombinantly produced, as it folds properly. Kim *et al.* teach that their experiments suggest that both Ig domains of p58 are necessary for HLA-C binding and that the binding site on KIR might be the exposed region at the interface between the N- and C-terminal γ domains (see entire reference, especially paragraph spanning columns 1-2 on page 3879). Kim *et al.l* teach anti-p58 KIR mAbs that were found to interfere with class-I-mediated protection of

target cells, *i.e.*, they are capable of neutralizing KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing p58 (especially page 3876).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made more mAbs by the conventional hybridomas technology taught by Shin *et al.*, including to have used the γ2 and γ 3 domain peptide as the immunogen, to have tested and selected for antibodies that bind to both KIR2DL1 and to KIR2DL2/3 and to have further tested these antibodies for the ability to neutralize KIR-mediated inhibition of NK cell cytotoxicity.

The position of the Examiner is respectfully traversed. Contrary to the rejection, the primary reference, Shin *et al.*, does not teach or suggest the claimed invention. The reference fails to do so as it does not teach or suggest any antibodies possessing the recited specific combination of binding and functional properties recited in Claims 88 and 90. Rather, Shin *et al.* report a number of antibodies that **are not cross-reactive with both KIR2DL1 and KIR2DL2/3** (see, *e.g.*, Table 1 and page 524 of Shin *et al.*). In addition, Shin *et al.* clearly teach that GL183 and EB6 do not bind to both KIR2DL1 and KIR2DL2/3. Moreover, while Shin *et al.* also report two antibodies, A210 and A803g, that *do* bind both KIR2DL1 and KIR2DL3, *neither of them inhibited a KIR2DL*, as summarized by the following passages:

Previously, we obtained three recombinant P58 KIR or p50 KAR proteins, KAR-K1 (KIR2DS4), KIR-K6 (KIR2DL1), and KIR-K7 (KIR2DL3)....while A210 and A803g bound to all three recombinant proteins. (see Shin *et al.*, Abstract, lines 3-8)

Among the existing MAbs, EB6 and GL183 are able to interfere with the binding between p58 KIR and HLA-C and to block the inhibitory signal transmitted through p58 KIR (6-8). So NK cytotoxicity is increased when EB6 or GL183 is added to a co-culture system of NK cells and HLA-C expressed target cells (6-8). With the MAbs produced in this study, it was examined whether MAbs could interfere with the binding between p58 KIR and HLA-C. **However, no MAbs interfered with the binding or blocked the inhibitory signal transmitted through p58 KIR (data not shown). Moreover, broad reactivity in our MAbs implied that**

their epitopes did not exist on the HLA-binding region in p58 KIR. (emphasis added; see Shin *et al.*, page 526, first full paragraph).

Accordingly, Shin *et al.*, at least taken lone, would not motivate one of ordinary skill to produce antibodies according to the invention, nor would the reference provide any expectation that antibodies possessing the recited combination of binding and functional properties could be obtained. Essentially, while Shin *et al.* would arguably suggest that antibodies may be obtained that bind to both KIR2DL1 and KIR2DL3, this reference discloses that such antibodies would not inhibit KIR2DL-mediated inhibition of NK cytotoxicity. Whether other antibodies could be produced via hybridoma technology is not disputed. However, this is irrelevant, absent any reasonable expectation to obtain antibodies as claimed. Shin *et al.* would provide no expectation that antibodies which bind to a conserved epitope in KIR2DL1 and KIR2DL3, as claimed, would further be capable of neutralizing or inhibiting KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing any of the following (i) KIR2DL1, (ii) KIR2DL2/3, or (iii) a combination of KIR2DL1 and KIR2DL2/3.

The deficiencies of Shin *et al.* are not cured by Kim *et al.* Kim *et al.* also does not teach any antibodies which bind to a conserved epitope in KIR2DL1 and KIR2DL3 as claimed, and neutralize or inhibit KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing any of the following (i) KIR2DL1, (ii) KIR2DL2/3, or (iii) a combination of KIR2DL1 and KIR2DL2/3.

The Office Action again asserts that Kim *et al.* teach anti-p58 KIR mAbs that interfere with class I-mediated protection of target cells, *i.e.*, they are capable of neutralizing KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing p58 (especially page 3876). The Office Action further argues that although the reference does not explicitly teach that the neutralizing anti-p58 mAbs bind to KIR2DL1 and KIR2DL2/3, that the Shin *et al.* reference teaches that a mAb that has its epitope in the HLA-binding region in p58 KIR may be the most effective mAb for blocking the interaction between p59 KIR and HLA-C, and further teaches that the HLA-C recognizing receptor which is inhibitory, is the p58 KIR belonging to KIR2DL group

comprised of KIR2DL1 and KIR2DL2/3. Therefore, the Office Action alleges that the claimed antibody appears to be the same or "similar" to the antibody of the prior art absent a showing of differences. The Examiner suggests that a comparison be provided to substantiate patentable differences and relies upon In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Applicants respectfully disagree with the stated basis for the obviousness rejection.

Applicants again respectfully note that Kim *et al.*, similar to Shin *et al.*, does not teach, report or use any antibodies as claimed. Rather, Kim *et al.* teach only the use of recombinant KIR and HLA-C proteins. Also, Applicants note that Kim *et al.* makes reference to previous literature studies that reportedly use antibodies that bind to KIR (see, for example, the passage at page 3876 emphasized in the Office Action). Particularly the passage at page 3876 of Kim *et al.*, to which the Office Action again refers, cites references numbered 22, 23 and 36, which respectively correspond to Moretta *et al.* (1993) J. Exp. Med. 178: 597, Vitale *et al.* (1995) P.N.A.S. USA 92:3536 and Ciccone *et al.* (1994) Eur. J. Immunol. 24:1003. However, in contradistinction to the rejection, this passage refers solely to two antibodies, EB6 and GL183, which do *not* bind *both* KIR2DL1 and KIR2DL2/3 as evidenced by the text reproduced below (emphasis added):

Human NK clones can be grouped according to their HLA-C recognition and Ab-binding properties (22). A group of NK clones that is reactive with **mAb EB6** recognizes HLA-Cw4 and related alleles, including HLA-Cw2, -Cw5, and -Cw6. A second group of NK clones reactive with **mAb GL183** recognizes HLA-Cw3 and related alleles, including HLA-Cw1, -Cw7, and -Cw8 (22, 23, 33, 34). NK clones negative for p58 KIRs were also found to be specific for different alleles of class I MHC molecules (35). **Specific interaction between HLA-C and p58 KIRs was suggested by Ab blocking experiments (22, 23, 36).** Either anti-class I MHC or anti p58 KIR mAbs were found to interfere with class I MHC-mediated protection of target cells. Direct evidence for specific recognition of target cells by NK receptors was provided by the binding of a soluble form of p.58 KIRs to cells transfected with the cognate HLA-C subtype (26) and by direct binding between a recombinant soluble p58 KIR and recombinant soluble HLA-Cw4 (37). The soluble KIR forms a 1:1 complex with the HLA-Cw4 molecule.

With particular regard to cited references 22, 23 and 36, Moretta *et al.* (1993), submitted in an Information Disclosure Statement (IDS) dated September 21, 2006, makes use of EB6 and GL183 (and XA141, an IgM specific for the EB6 molecules, see abstract). Vitale *et al.* (1995), provided with the accompanying IDS, uses the same EB6, GL183 (and XA-141) antibodies as Moretta (1993). Finally, Ciccone *et al.* (1994), also provided with the accompanying IDS, did not use anti-KIR antibodies but rather anti-HLA-C antibodies 6A4 and A6-136 mAb, which respectively bind HLA-Cw4 or HLA-Cw3. Consequently, Kim *et al.* refers exclusively to antibodies EB6 and/or GL183, both of which have been previously discussed in Applicants' responses dated December 2, 2010 and October 28, 2010. EB6 binds KIR2DL1 but *not* KIR2DL2/3. GL183 in turn binds KIR2DL2/3 but *not* KIR2DL1 (see paragraph bridging pages 524-525 of Shin *et al.*). Kim et al. therefore does not anticipate or render obvious the present claims which require binding to both KIR2DL1 and KIR2DL2/3.

Therefore, Kim *et al.*, alone or in combination with Shin *et al.*, does not provide any motivation to make antibodies as claimed as the reference similarly would provide no reasonable expectation of success. Particularly, the reference does not teach or suggest any antibodies meeting the limitations of the claimed invention as set forth in Claims 88 and 90, or suggest that they could be obtained by any amount of experimentation. Indeed, Kim *et al.* reports experiments conducted purportedly in order to better elucidate how the Ig domains of p58 are involved in HLA-C binding. However, the reference provides no information that would suggest that antibodies as claimed herein could be produced that bind to both KIR2DL1 and KIR2DL2/3, which neutralize or inhibit KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing any of the following (i) KIR2DL1, (ii) KIR2DL2/3, or (iii) a combination of KIR2DL1 and KIR2DL2/3. Rather, Kim *et al.* substantiates Applicants' position that the claimed antibodies are non-obvious as their combination of specific binding and functional properties, as recited in the current pending claims, is non-obvious from Kim *et al.*

The non-obviousness of the claimed invention is actually supported by Kim *et al.* For example, Kim *et al.* concedes that their experiments did not confirm the binding site on KIR that is involved in HLA-C binding. Rather, as acknowledged by the text quoted by the Examiner,

Kim *et al.* postulated that it (the binding site) "might" be an exposed region at the interface between the N- and C-terminal γ domains. This uncertainty even as to how the receptors interact with HLA-C molecules further supports Applicants' view that Shin *et al.* and Kim *et al.*, separately or in combination, provide no suggestion or reasonable expectation that any monoclonal antibodies could be obtained as claimed which bind a conserved epitope on KIR2DL1 and KIR2DL2/3, and which further neutralize KIR2D-mediated inhibition of NK cell cytotoxicity by NK cells expressing KIR2DL1, KIR2DL2/3, or a combination thereof.

Applicants' disclosure at page 25 also does not support the rejection. The subject application teaches a monoclonal antibody DF200 that possesses the binding and functional properties recited in Claims 88 and 90. As noted by the Examiner at page 25, the application explains on this page and other places in the specification what is meant by "inhibit or neutralize KIR-mediated inhibition of cytotoxicity" in the context of the invention: The Examiner suggests based on the teachings in this application that the antibody of the invention "appears to be similar to the antibody of the prior art absent a showing of unobvious differences".

However, the position taken by the Examiner is respectfully submitted to be improper. The cited references unequivocally state, or cite to references that establish, that none of the antibodies disclosed or referenced therein inherently meet the limitations of Claims 88, 90 and 91. The Examiner has provided no valid basis for concluding that any monoclonal antibody disclosed or suggested by Shin *et al.* or Kim *et al.*, whether the references are considered alone or in combination, binds to a conserved epitope on KIR2DL2 and KIR2DL2/3, and inhibits or neutralizes KIR2D-mediated inhibition of NK cell cytotoxicity as defined in the subject specification.

As noted above, Applicants acknowledge that their disclosure at page 25 defines the meaning of "neutralize" or "inhibit" KIR-mediated inhibition of NK cell cytotoxicity". However, this disclosure does not support a conclusion that the Shin *et al.* or Kim *et al.* references teach or suggest an antibody having the claimed binding specificity and functional activity.

Also, the Examiner's reliance again on In re Best, 586 F.2d 1252, 195 USPQ 430 (CCPA

1977), is misplaced. Obviousness requires a teaching or suggestion of all limitations in a claim. *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974)). Applicants respectfully submit that they have already provided convincing evidence, contained in the very references relied upon by the Examiner, and/or references cited therein (see supra), which support a conclusion that these references do not teach or suggest an antibody as claimed. Therefore, the Examiner's reliance on the In re Best 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) decision is misplaced as she has pointed to no antibody in either Shin *et al.* or Kim *et al.* that is sufficiently "similar" to the claimed antibodies, so as to render the claims unpatentable under obviousness grounds. Particularly, the Examiner cannot dismiss the fact that the subject claims require a specific combination of binding and functional activities. There is absolutely no basis for concluding that any antibody in the cited prior art inherently possesses the same properties. The Examiner cannot shift the burden to Applicants without some basis for asserting that any antibody in the prior art reads on the claimed antibodies. Applicants respectfully submit that the rejection must be vacated as the Examiner has not met her burden.

Applicants again note that the claims under active consideration are directed to antibodies possessing a specific combination of properties. Whether antibodies in the cited references possess one of the recited properties does not render unpatentable the subject claims, especially when Applicants have established that the prior art antibodies do not possess the recited combination of properties.

Also, the rejection cannot be predicated on the fact that Applicants obtained their antibodies by use of hybridoma technology. Indeed, if this were the standard for patentability of a novel antibody (that it was not obtained by use of hybridoma technology) virtually no monoclonal antibodies possessing novel binding and/or functional properties would be patentable as most antibodies even today are derived by hybridoma technology. (It is noted that some antibodies are alternatively produced by SLAM (Single Lymphocyte Antibody Manufacture) which method does not require the formation of hybridomas).

The reasoning of the Examiner is respectfully submitted to be improper. The fact that the prior art may have used similar methods to make hybridomas secreting antibodies against KIR receptors and were not successful in producing any antibodies that meet the limitations of the claims proves Applicants' point that the result was not predictable from the cited references.

Also, the fact that Applicants were successful using assertedly similar methods cannot be used in support of an obviousness rejection. As noted, the Examiner is improperly attempting to argue that Applicants' success is indicia of the obviousness and expectation of success of the invention. However, this reasoning is clearly erroneous as the Examiner cannot use Applicants' disclosure against the claims as this does not constitute prior art. The prior art must establish the expectation of success in the absence of any reliance on Applicants' specification.

With respect thereto, Applicants again note that all of the claims under examination require antibodies or antibody fragments that bind a conserved epitope on KIR2DL2 and KIR2DL2/3 that neutralize or inhibit KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing any of the following (i) KIR2DL1, (ii) KIR2DL2/3 and (iii) a combination of KIR2DL1 and KIR2DL2/3. Nothing in either of the cited references teaches or suggests a monoclonal antibody could be produced having this binding specificity that would inhibit or neutralize KIR-mediated cytotoxicity by these 3 distinct subsets of NK cells as claimed herein.

Applicants again respectfully submit that the rejection must be vacated as it is clearly improper. A proper obviousness rejection requires that the cited reference or references motivate a skilled artisan to make the invention with a reasonable expectation of success. It can not be a mere "fishing expedition". Herein the references separately or in combination would not motivate a skilled artisan to make the claimed antibodies as it could not have been reasonably anticipated that antibodies binding to a conserved epitope on KIR2DL2 and KIR2DL2/3 would inhibit or neutralize KIR2D-mediated inhibition of NK cell cytotoxicity, much less suggest that monoclonal antibodies could be obtained which would neutralize or inhibit KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing any of the following (i) KIR2DL1, (ii) KIR2DL2/3, or (iii) a combination of KIR2DL1 and KIR2DL2/3.

Again, Applicants respectfully note that the fact that Applicant was successful using assertedly similar methods cannot be used in support of an obviousness rejection. This reasoning is legally erroneous as the Examiner cannot use Applicants' disclosure against the claims as this does not constitute prior art. The prior art, not Applicants' specification, must establish the expectation of success, i.e., in the absence of any reliance on Applicants' specification.

Based on the foregoing, withdrawal of the instant obviousness rejection of Claims 88, 90 and 91 is respectfully requested.

Traversal of Rejection of Claims 88-91 Under 35 USC § 103 (a) As Assertedly Being Obvious Based on Shin et al. in view of Kim et al., and in view of alleged admissions in the specification on page 25 at lines 15-28 and in the paragraph spanning pages 25-26 and Harlow and Lane (of record).

Claims 88-91 are also rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Shin *et al.* in view of Kim *et al.*, and in view of alleged admissions in the specification on page 25 at lines 15-28 and at the paragraph spanning pages 25-26 and further in view of Harlow and Lane.

The rejection is the same as the previous rejection except that Harlow and Lane is relied upon for the disclosure relating to the use of PBS and similar isotonic solutions for formulating antibodies.

This rejection is respectfully traversed for the same reasons as the above-traversed rejection of clams 88, 90 and 91. For the same reasons, Kim *et al.* and Shin *et al.*, separately or in combination, do not teach or suggest that antibodies could be obtained possessing the binding and functional properties recited in Claims 88 and 90. Also, the Examiner is not permitted to support the rejection by reliance on Applicants' specification as this does not constitute prior art.

The addition of Harlow and Lane does not bolster the rejection as it similarly contains no teaching or suggestion which would motivate a skilled artisan, or provide a reasonable expectation of success, of obtaining antibodies as claimed that bind to a conserved epitope on

KIR2DL2 and KIR2DL2/3, that inhibit or neutralize KIR2D-mediated inhibition of NK cell cytotoxicity. Certainly, the references would in no way suggest that monoclonal antibodies as claimed could be obtained which neutralize or inhibit KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing any of the following (i) KIR2DL1, (ii) KIR2DL2/3, or (iii) a combination of KIR2DL1 and KIR2DL2/3. Rather, Harlow and Lane merely teach the use of various excipients for storing antibodies.

Therefore, for the foregoing reasons, the instant obviousness rejection of Claims 88-91 under 35 U.S.C. § 103(a) as allegedly being obvious over Shin *et al.*, (Hybridoma, 18(6):521-527 (1999)) in view of Kim *et al.* (J Immunol. 159:3875-3882(1997)), and further in view of alleged admissions in the specification on page 25 at lines 15-28 and at the paragraph spanning pages 25-26 and still further in view of Harlow and Lane should be withdrawn.

Traversal of Rejection of Claims 88-91 Under 35 USC § 103 (a) As Assertedly Being Obvious Over Spaggiari et al. in view of Harlow and Lane, as Allegedly further evidenced by Serotec and Alleged Admissions in the Specification on Page 62, at lines 4-5 and 9.

Claims 88-91 also stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Spaggiari in view of Harlow and Lane, as allegedly further evidenced by Serotec and "admissions" in the specification on page 62 at lines 4-5 and 9. This rejection is respectfully traversed.

For the same reasons set forth above, Spaggiari *et al.* fails to teach or suggest a human, chimeric or humanized antibody possessing the binding and functional properties set forth in Claims 88 and 90. The reference fails to do so, because, while allegedly suggesting an antibody that binds to both KIR2DL2 and KIR2DL2/3, the reference contains no information that would suggest to a skilled artisan that this antibody or any other antibody which binds to both KIR2DL1 and KIR2DL2/3 would be capable of neutralizing or inhibiting KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing any of the following (i) KIR2DL1, (ii) KIR2DL2/3, or (iii) a combination of KIR2DL1 and KIR2DL2/3.

The AbD Serotec reference cannot be relied upon in the obviousness rejection other than to establish inherency. Accordingly, its alleged teachings as to the effects of NKVFS1 on the inhibition of KIR-mediated NK cytotoxicity cannot be considered in the obviousness rejection.

Absent this alleged teaching, there would have been no reasonable expectation from the Spaggiari reference, even assuming for the sake of argument that the NKVFS1 antibody had been publicly available, that this antibody, or another antibody capable of binding both KIR2DL2 and KIR2DL2/3, would be capable of neutralizing or inhibiting KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing any of the following (i) KIR2DL1, (ii) KIR2DL2/3, or (iii) a combination of KIR2DL1 and KIR2DL2/3. Indeed, the state of the prior art at the time of the present invention would have reasonably suggested that such an antibody would likely NOT be capable of neutralizing or inhibiting KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing (i) KIR2DL1, (ii) KIR2DL2/3, or (iii) a combination of KIR2DL1 and KIR2DL2/3. This reasonable expectation is supported by references discussed supra, i.e., Shin *et al.* and Kim *et al.* As discussed above, while Shin *et al.* discloses 2 antibodies that bind to KIR2DL1 and KIR2DL2/3, neither of these antibodies neutralizes or inhibits KIR-mediated inhibition of NK cell cytotoxicity. This would suggest to one of ordinary skill that the conserved or homologous epitope in KIR2DL1 and KIR2DL2/3 to which antibodies may bind is likely not involved in KIR-mediated inhibition of NK cell cytotoxicity in NK cells, or alternatively suggest that blocking this site would not be sufficient to neutralize or inhibit KIR-mediated inhibition of NK cell cytotoxicity. In addition, Kim *et al.* also does not teach or suggest such an antibody. Rather, while Kim *et al.* refers to other anti-KIR2DL antibodies, as evidenced by the discussion supra relating to this reference, none of these prior art antibodies possesses the combination of binding and functional properties of the claimed antibodies.

Applicants respectfully submit that absent a reasonable expectation that the antibody of Spaggiari would inherently be capable of neutralizing or inhibiting KIR-mediated inhibition of NK cell cytotoxicity, there would have been no incentive for a skilled artisan to produce human, humanized or chimeric antibodies or antibody fragments derived therefrom potentially possessing the recited combination of binding and functional properties (set forth in Claims 88

and 90). Likewise Applicants' disclosure at page 62 does not support the obviousness rejection. Foremost, this disclosure does not substantiate the public availability of the Spaggiari NKVFS1 antibody, and moreover provides no suggestion that it had been publicly known, prior to the effective filing date of this application, that the NKVFS1 antibody neutralizes or inhibits KIR-mediated inhibition of NK cell cytotoxicity. In fact, had this been known, more likely than not Spaggiari would have noted this fact in the Spaggiari reference cited in the rejection. Tellingly the reference is silent in this regard.

Also, Serotec cannot be relied upon as it can only be used to support inherency, not obviousness as it was published after the effective filing date of this application. The primary reference does not teach or suggest any human, chimeric or humanized antibodies, much less antibodies that inherently possess the properties of the claimed genus of antibodies as set forth in Claims 88 and 90. As noted above, Applicants' disclosure at page 62 does not suggest the public availability of the Spaggiari NKVFS1 antibody, nor does it suggest that this antibody had been known to inhibit KIR2D-mediated inhibition of NK cytotoxicity as claimed.

The addition of Harlow and Lane does not remedy the deficiencies of the foregoing references as Harlow and Lane also fail to teach or suggest chimeric, human or humanized antibodies or antibody fragments possessing the claimed combination of binding and functional properties. Rather, they merely suggest that the formulation of antibodies in PBS or another acceptable carrier was known as of the date of the invention. This is not disputed. However, the rejection is unsustainable as none of the references would direct a skilled artisan to make and formulate chimeric, human or humanized antibodies or fragments thereof as claimed.

Based on the foregoing, withdrawal of the instant obviousness rejection of Claims 88-91 is respectfully requested.

Traversal of Rejection of Claims 88, 90 and 91 Under 35 USC § 103 (a) as Assertedly Being Obvious Over Shin et al. in view of Kim et al. and Winter and Long (J Immunol. 158:4026-8 (1997)) in View of Alleged Admissions in the specification on page 25 and 26.

Claims 88, 90 and 91 also stand rejected under 35 USC § 103(a) as allegedly being obvious over Shin *et al.*, (Hybridoma, 18(6):521-527 (1999)) in view of Kim *et al.* (J Immunol. 159:3875-3882(1997)), and Winter and Long (J. Immunol. 158:402608 (1997)), hereinafter "Winter and Long," as allegedly supported "admissions" in the specification on page 25 at lines 15-28 and in the paragraph spanning pages 25-26. This rejection is respectfully traversed.

Shin *et al.* and Kim *et al.* are relied upon as set forth in the prior traversed rejections based on these references. The Examiner states the following with respect to the Winter and Long reference:

Winter and Long teach that changing a single amino acid residue between the p58 KIR (*i.e.*, KIR2DLA and KIR2DL2/3) correlated with a switch in the specificity of each from HLA-Cw*04011 to HLA-C2*304, and vice versa. Winter and Long teach that this amino acid position is the first Ig domain of these KIR that determines their ability to discriminate between the two groups of HLA-C allotypes. Winter and Long also teach that the two p58 receptors differ by only 17 amino acid residues in their extracellular region, with five of eleven amino acid differences upstream of the second Ig domain potentially accounting for the specificity of KIR binding to the HLA-Cw3 vs HLA-Cw4 cluster (especially abstract, introduction, Figures 1 and 3, results and discussion at the first paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made more Mabs by the conventional hybridoma methodology taught by Shin *et al*, including using the γ2 and γ3 domains as an immunogen, to have tested and selected for antibodies that bind to both KIR2DL1 and to KIR2DL2/3 and to have further tested these antibodies for the ability to neutralize KIR-mediated inhibition of NK cell cytotoxicity.

For the same reasons set forth above, Shin *et al.* alone or in combination with Kim *et al.* would not motivate one of ordinary skill to produce antibodies having the claimed combination of antigenic binding specificity and functional activity. To the contrary, Shin *et al.* does not each any antibodies as claimed. This is absolutely clear upon review of the reference and the disclosed description of their monoclonal antibodies. Particularly, they teach a number of antibodies that **are not cross-reactive with both KIR2DL1 and KIR2DL2/3** (see, *e.g.*, Table 1 and page 524 of Shin *et al.*). For example, they clearly teach that GL183 and EB6 do not bind to both KIR2DL1 and KIR2DL2/3. Also, while they do identify two antibodies, A210 and A803g, that *do* bind both KIR2DL1 and KIR2DL3, *neither of them inhibited a KIR2DL*, as summarized by the following passages:

Previously, we obtained three recombinant P58 KIR or p50 KAR proteins, KAR-K1 (KIR2DS4), KIR-K6 (KIR2DL1), and KIR-K7 (KIR2DL3)....while A210 and A803g bound to all three recombinant proteins (see Shin *et al.*, Abstract, lines 3-8).

Among the existing MAbs, EB6 and GL183 are able to interfere with the binding between p58 KIR and HLA-C and to block the inhibitory signal transmitted through p58 KIR (6-8). So NK cytotoxicity is increased when EB6 or GL183 is added to a co-culture system of NK cells and HLA-C expressed target cells (6-8). With the MAbs produced in this study, it was examined whether MAbs could interfere with the binding between p58 KIR and HLA-C. **However, no MAbs interfered with the binding or blocked the inhibitory signal transmitted through p58 KIR (data not shown)...Moreover, broad reactivity in our MAbs implied that their epitopes did not exist on the HLA-binding region in p58 KIR.** (emphasis added; see Shin *et al.*, page 526, first full paragraph).

Accordingly, Shin *et al.* would provide no expectation that the use of standard hybridoma technology would have given rise to antibodies as claimed. There is nothing in Shin *et al.* which would suggest that antibodies that cross-react with a conserved or homologous epitope present in KIR2DL1 and KIR2DL3, would further inhibit the KIR-induced inhibition of activation of NK cells as claimed. Also, for the same reasons set forth above Kim *et al.* does not cure the

deficiencies of Shin *et al.* It also fails to teach or suggest antibodies as set forth in Claims 88 and 90, or the claims dependent thereon.

The addition of the Winter and Long teachings is also not suggestive of the invention. Essentially, the reference is relied upon based on its disclosure as to sequence similarities between the KIR2DL1 and KIR2DL2/3 receptors at the amino acid level, including a specific residue which if changed may alter the specificity of KIR binding to HLA-C molecules. While these teachings are of scientific interest insofar as KIR-binding to HLA-C molecules, this teaching does not support the rejection as this information would not reasonably suggest that monoclonal antibodies having the recited binding and functional properties could have been obtained. While these receptors admittedly are somewhat conserved in structure, this would not provide a reasonable expectation that antibodies that cross-react with a common epitope present in both of these receptors would inhibit KIR2D-mediated inhibition of NK cytotoxicity. Rather, it was reasonable to assume based on Kim *et al.* and Shin *et al.* that antibodies that bind to a common epitope on these receptors, if produced, would not inhibit of KIR2D-mediated cytotoxicity, e.g., these antibodies may have permitted HLA-C ligand binding to these receptors or the antibodies may not bind with suitable binding affinity to NK cells expressing KIR2DL1 or KIR2DL2/3, or a combination thereof, so as to inhibit KIR2D-mediated inhibition of NK cytotoxicity.

Applicants' disclosure at pages 25 and 26 also does not support the rejection. Therein Applicants disclose what is intended by "inhibit or neutralize" KIR2D-mediated inhibition of NK cytotoxicity. With respect thereto, it should be noted that Claims 88 and 90 require that the claimed antibodies inhibit KIR2D-mediated cytotoxicity by NK cells expressing either KIR2DL1 or KIR2DL2/3 or a combination thereof. This property of the claimed antibodies is not suggested by the prior art, nor would the prior art provide a reasonable expectation that antibodies possessing these inhibitory properties could have been obtained by use of hybridoma technology.

Accordingly, reconsideration and withdrawal of the instant obviousness rejection of Claims 88, 90 and 91 is respectfully requested.

Traversal of Rejection of Claims 88-91 Under 35 USC § 103 (a) as Assertedly Being Obvious Over Shin et al. in view of Kim et al. and Winter and Long in View of Alleged Admissions in the Specification on page 25 and 26 and Harlow and Lane.

Claims 88-91 also stand rejected under 35 USC § 103(a) as allegedly being obvious over Shin *et al.* in view of Kim *et al.*, Winter and Long, alleged "admissions" in the specification on page 25 at lines 15-28, and the Harlow and Lane reference.

This rejection is substantially the same as the prior rejection except that Harlow and Lane is relied upon to suggest pharmaceutical compositions containing antibodies that comprise excipients such as PBS and similar isotonic solutions. The addition of this reference similarly does not cure the deficiencies of the rejection. Essentially the references separately or in combination fail to motivate a skilled artisan to make human, humanized or chimeric monoclonal antibodies or fragments thereof having the antigenic specificity and functional properties recited in Claims 88 and 90.

Accordingly, withdrawal of this rejection of Claims 88-91 is respectfully requested.

Traversal of Provisional Double Patenting Rejection of Claims 70-79, 81 and 83-91 Over Claims 3-4 and 5-7 of Commonly Assigned US Serial No. 12/813,040.

Claims 70-79, 81 and 83-91 also stand provisionally rejected on double patenting grounds over claims 3-4 and 5-7 of commonly assigned US Serial No. 12/813,040. The Examiner is respectfully requested to hold this rejection in abeyance until this application is otherwise in condition for allowance.

Conclusion

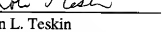
In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

If the Examiner has any questions relating to this Reply she is respectfully requested to contact the undersigned so that prosecution may be expedited. Respectfully submitted,

HUNTON & WILLIAMS

Date: October 17, 2011

By: 

Robin L. Teskin
Registration No. 35,030

HUNTON & WILLIAMS LLP
INTELLECTUAL PROPERTY DEPARTMENT
2200 PENNSYLVANIA AVE NW
WASHINGTON DC 20037-1701
(703) 714-7645 (telephone)
(202) 778-2201 (facsimile)

RLT/dkt